

ORTHOPAEDIC and REHABILITATION DEVICES PANEL MEETING
June 2, 2006

2nd Mail-out Documents

Dear Panel Members,

Please find attached additional public comments for your review. These comments were made in reference to the Friday, June 2, 2006 meeting of the Orthopaedic and Rehabilitation Devices Panel and were received after the April mail-out. This information is in the process of being posted to the petition docket 2005P-0121.

(<http://www.fda.gov/ohrms/dockets/dockets/05p0121/05p0121.htm>)

Attachments:

1. RS Medical Comments (April 29, 2006)
 - a. Signal "Transduction in Electrically Stimulated Bone Cells; Brighton et al, The Journal of Bone and Joint Surgery, Incorporated, 2001.
2. BGS Reclassification Opposition Group Comments (May 15, 2006)
3. Arthur A. Pilla, PhD Comments and Literature (1) (May 17, 2006)
 - a. "Mechanism and Therapeutic Applications of Time-Varying and Static Magnetic Fields," In: Handbook of Biological Effects of Electromagnetic Fields, 3rd Ed., Barnes, F., Greenbaum, B, eds., CRC Press, 2006, in press.
4. RS Medical Comments and Literature (2) (May 18, 2006)
 - a. Wang, Z, Clark, CB, and Brighton, CT, "Up-Regulation of Bone Morphogenic Proteins in Cultured Murine Bone Cells with Use of Specific Electrical Fields," The Journal of Bone and Joint Surgery, 88A: 1053-1065, 2006.
 - b. Brighton, CT, "Advanced Clinical Applications of Electromagnetic-Field Effects," In: Electromagnetics in Biology and Medicine, Brighton, CT and Pollack, SR, eds., San Francisco Press, 293- 30, 1991

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(HFZ-305)

Re: FDA Docket 2005P-0121/CCP; Response to Comments on RS Medical's Petition to
Reclassify Non-Invasive Bone Growth Stimulator

Dear Sir or Madam:

This document is submitted on behalf of RS Medical, of Vancouver, Washington, and responds to comments on the reclassification petition, cited above, submitted by Hogan & Hartson, LLP on February 17, 2006, and by King & Spalding, LLP on February 10 and March 7, 2006.

Both of these law firms represent companies who hold approved premarket approval applications (PMAs) for devices that fall within the Non-Invasive Bone Growth Stimulator type of device; the type of device that is the subject of the reclassification petition. The companies who hold these approved PMAs are opposed to reclassification, and refer to themselves as the "BGS Reclassification Opposition Group (BGS Group)."

It is well known that PMA holders see the requirement for PMA approval as an impediment to competition. They also see the PMA requirement as a reasonable hurdle for newcomers to their field. This sentiment is based on the fact that the PMA holders themselves were required to obtain PMA approval, and this process generally requires more testing, and a longer FDA review period, than the premarket notification [510(k)] process applicable to Class I and II devices. Put succinctly, the PMA holders have a significant financial interest in keeping the Non-Invasive Bone Growth Stimulator in Class III. The comments submitted on their behalf

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appear to be an effort to protect the group's financial interests, as opposed to their promoting a serious discourse on the issues.

We have attempted to condense the opposition's comments in the enumerated statements provided below; following each statement is a brief response.

1. The opposition argues that by seeking to have the Non-Invasive Bone Growth Stimulator reclassified, RS Medical is trying to make an "end run" around its regulatory responsibility to submit a PMA.

Specifically, the opposition group argues that "RS Medical has sought to evade FDA's . . . premarket requirements" and urges that the Agency "not countenance this attempted end-run of the regulations."¹ Reclassification, however, is a legitimate process that may be explored by any interested person - - it is not an illegitimate means of avoiding premarket approval. The option of reclassification was deliberately included in the Medical Device Amendments of 1976 (MDA),² and Congress clarified and simplified the rules for reclassification in the Safe Medical Devices Act of 1990 (SMDA).³ Congress was motivated by a desire to "permit more efficient regulation,"⁴ and hence wished to discourage the imposition of Class III controls where Class I or II controls would suffice.⁵ For that reason, Congress directed that devices that were initially subjected to Class III controls be reclassified to Class I or II if information becomes available showing that their safety and effectiveness can be ensured through regulation in the less

¹ Comment of BGS Group, dated February 10, 2006, at 10.

<http://www.fda.gov/ohrms/dockets/dockets/05p0121/05p-0121-c000009-vol3.pdf>.

² The MDA is replete with provision for reclassification, depending on the circumstances applicable to the device: Sections 513(e), 513(f), 514(b), 515(b), and 520(l).

³ Prior to the SMDA, Section 513(e) of the Food, Drug, and Cosmetic Act (FDCA) permitted reclassification by the issuance of a regulation, but made no mention of the criteria for reclassification. The SMDA amended section 513(e) by adding specific criteria for the reclassification of a Class III device into Class I or II. These criteria are described in detail in the response to item number 6.

⁴ 136 Cong. Rec. S17456-01 (daily ed. October 27, 1990) (statement of Senator Kennedy).

burdensome classification.⁶ RS Medical's use of the petition process is thus not an attempt to make an "end run" around the regulatory scheme, but rather an implementation of the regulatory framework as Congress envisioned it.

2. The comments assert that RS Medical refuses to submit information that is unfavorable to the petition.

RS Medical has performed a number of extensive literature searches for information pertinent to the reclassification issues, both in its initial petition and in response to FDA's "Points to Consider" document. RS Medical has described its methodology for searching databases; explained the criteria that were used to include and exclude certain literature articles; and, cited all articles that are pertinent. **The opposition has not found fault with RS Medical's methodology, nor has it cited any so-called "unfavorable" information that should have been included in the petition.**

3. The comments maintain that the articles that show that an unsafe or ineffective signal can be developed are "unfavorable" and indicate that Class II controls are insufficient.

As RS Medical explained in its most recent amendment to the petition, articles that discuss an ineffective, or unsafe, signal are not unfavorable - - **unless** the article shows that an existing approved device proposed for reclassification is unsafe or ineffective. If an article shows that an actual device to be reclassified is unsafe or ineffective, it should be considered unfavorable because it potentially indicates that such a device should not be marketed or serve as a predicate device for new devices of the same type. On the other hand, an article should not be deemed

⁵ "H.R. 11124 proposes that all medical devices be classified into one of three regulatory categories **depending on the extent of regulation necessary to assure safety and effectiveness.**" (Emphasis added; Ibid., page 12.)

⁶ "By regulation ...the Secretary may change the classification of a device from class III ...to class II if the Secretary determines that special controls would provide reasonable assurance of the safety and effectiveness of the device" (Section 513(e) of the FDCA, 21 U.S.C. § 360c.)

unfavorable if it only shows that an unsafe or ineffective device can be designed. One can design an unsafe or ineffective anesthesia machine, vascular graft, daily wear contact lens, heating blanket, hospital bed, etc. Showing that one can design a flawed device, however, is not evidence that the device should be regulated in Class III, and, therefore, an article demonstrating this should not be considered unfavorable for purposes of reclassification. On the contrary, when an article identifies an unsafe or ineffective device through the application of preclinical, or limited clinical testing, the article is actually favorable. This is because the salient regulatory issue is whether an unsafe or ineffective device can be identified prior to marketing.

There is at least one article cited in the petition with equivocal results, and is available for analysis, regardless of whether it is characterized as “favorable” or “unfavorable.”

4. The opposition maintains that what it refers to as unfavorable data should be applied to all Non-Invasive Bone Growth Stimulators just as RS Medical applies favorable data to the device in general.

Specifically the opposition states:

...in the case of favorable data, the company finds it unnecessary to specify the particular devices being tested. In contrast, in studies that produce unfavorable data, RS Medical attributes the results to a specific device, and does not generalize to all types of noninvasive bone growth stimulators.⁷

“Favorable data,” which presumably are data showing that some Non-Invasive Bone Growth Stimulator is safe and effective, need not be tied to a specific device because such data are only intended to establish that, as a general principle, the Non-Invasive Bone Growth Stimulator type of device can be safe and effective; and, such positive data do not in any way adversely reflect

on any specific device that is to be reclassified. Thus, the specific device in question need not be identified. In the case of data that show some specific device is ineffective or unsafe, the situation is different because it would be important to know if the device is one which is proposed for reclassification. Under the latter circumstances, RS Medical attempted to learn if an approved device was involved, in which case the data would have been unfavorable and RS Medical would then have identified it as such.

There is one small study that demonstrated mixed effectiveness results for a PEMF signal (Baker *et al*, 1984), and RS Medical attempted to learn whether a currently PMA-approved device was used. While the article did identify certain characteristics of the device, it was not clear that a PMA-approved device that is included in the reclassification petition was involved.

5. The comments contend that RS Medical has not identified the basic mechanism of action of the Non-Invasive Bone Growth Stimulator and, therefore, reclassification is inappropriate.

First, there is no requirement that the mechanism of action for a device be identified in order for it to be in Class II. To illustrate the point, there is some debate about the mechanism of action for the Implanted Peripheral Nerve Stimulator (21 C.F.R. §882.5870), the Implanted Spinal Cord Stimulator for Pain Relief (21 C.F.R. §882.5880), and the Transcutaneous Electrical Nerve Stimulator for Pain Relief (21 C.F.R. §882.5890). Nevertheless, all of these devices are in Class II.

Moreover, there is convincing evidence that both the capacitive coupling and inductive coupling devices included in the definition of the type of device to be reclassified have the same well-

⁷ Comments of EBI, LP, dated February 17, 2006, at 6.
<http://www.fda.gov/ohrms/dockets/dockets/05p0121/05p-0121-c000010-vol3.pdf>.

understood mechanism of action. Recent investigations⁸ have shown that both capacitive and inductive signals produce a significant increase in cell proliferation compared with controls. Signal transduction for capacitive coupling occurred by means of influx of calcium through voltage-gated calcium channels leading to an increase in intracellular levels of calcium, cytoskeletal calmodulin, and prostaglandin E₂. With inductive coupling, **signal transduction** is different. In this case, it causes an intracellular release of calcium leading to an increase in cytosolic calcium and an increase in activated cytoskeletal calmodulin.

Thus, although the initial events in these signaling cascades were different, the final pathway was the same, i.e., an increase in cytosolic Ca²⁺ and in activated cytoskeletal calmodulin. As such, both forms of electrical stimulation that are covered in the petition have a similar mechanism of action in promoting cellular proliferation in bone. (The cited article is attached.)

6. The opposition contends that information presented in the petition is inadequate because the specific characteristics of the devices being studied in the literature articles are not necessarily known.

The parties opposing RS Medical's petition have asserted that reclassification is not appropriate because the specific characteristics of the devices studied in the published literature are not well-described. Unlike the requirements for a PMA, however, there is no requirement that the literature relied upon in a down-classification petition contain a detailed characterization of the devices. Rather, it is sufficient if the literature concerns a generic "grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness."⁹

⁸ Signal Transduction in Electrically Stimulated Bone Cells; Brighton *et al*, The Journal of Bone and Joint Surgery, Incorporated, 2001. This article was not included in previous literature searches but was found with the "transduction" search term.

The opposition's reliance upon FDA's treatment of the down-classification petition for rigid gas permeable contact lenses is misplaced. They state:

In rejecting the down classification of rigid gas permeable ("RGP") contact lenses, FDA concluded that the literature in support of reclassification "requires detailed characterization of the lens or lenses from which the evidence is drawn and the lenses to which the characterization applies."

FDA's decision with respect to the reclassification of daily wear RGP lenses, however, is not relevant to the RS Medical petition. The RGP lens decision occurred in the 1980's, and was based upon the erroneous legal interpretation then being applied by the Agency that the reclassification process was very much like the PMA process. By the late 1980's, however, FDA began applying the reclassification provisions with an eye toward avoiding "overregulation." For example, in 1989, FDA granted a petition to down-classify poly(glycolide/L-lactide) absorbable surgical sutures from Class III to Class II and, in doing so, implicitly repudiated the position it had taken in the contact lens case. FDA's decision in the suture case was upheld by the courts.¹⁰

FDA's modification of its position with respect to down-classification is supported by the legislative history of the revisions to the reclassification provisions of the FDCA that were made by the Safe Medical Devices Act of 1990 (SMDA). Although the provision for reclassification was included in the 1976 MDA, the MDA did not set forth a standard for FDA to use in evaluating such petitions. In enacting the SMDA in 1990, Congress clarified and simplified the rules for reclassification. Specifically, the SMDA amended section 513(e) by adding the

⁹ See *Ethicon v. FDA*, 762 F. Supp. 382, 387 (D.D.C. 1991).

following statement:

By regulation promulgated under paragraph (1), the Secretary may change the classification of a device from class III—

(A) to class II if the Secretary determines that special controls would provide reasonable assurance of the safety and effectiveness of the device and that general controls would not provide reasonable assurance of the safety and effectiveness of the device, or

(B) to class I if the Secretary determines that general controls would provide reasonable assurance of the safety and effectiveness of the device. (21 U.S.C. § 360c(e), emphasis added.)

Congress revised section 513 in this way to make clear that down-classification is appropriate where a reasonable assurance of the safety and effectiveness of a generic class of devices can be assured through the use of general and special controls, and such assurance does not require that the agency conduct a premarket review of safety and effectiveness data related to a specific device. Such a review of device-specific data is, rather, what would be required in a PMA. The statutory change was made to allow FDA to avoid expending resources that would be required to review a PMA in situations where no PMA is necessary for an assurance that the device is safe and effective.¹¹

In short, to obtain down-classification of non-invasive bone growth stimulators, RS Medical is not obligated to provide literature that contains a “detailed characterization of the [devices] from which the evidence is drawn and the [devices] to which the characterization applies.” RS

¹⁰ *Id.*

¹¹ As the Conference Committee explained, “the reclassification of devices is an appropriate way to assure the FDA’s limited resources are allocated to the review and [regulation of] those devices which present the greatest risk.” House Report 101-808 at page 28, as reprinted in the U.S. Code Congressional and Administrative News at page 6322.

Medical's burden, rather, is to provide "sufficient information" about the generic class of devices for FDA to evaluate whether Class II controls are sufficient to provide assurance that the device is safe and effective"¹²

7. The comments contend that the literature articles on clinical trials provided in the petition are too diverse in study design to allow for pooling of the information, and thus do not constitute valid scientific evidence.

The petition is not a PMA, but a request for reclassification. As RS Medical's amendment of November 30, 2005 explained, data that might not be appropriate for inclusion in a PMA, may well be suitable for inclusion in a reclassification petition and, in fact, actually may serve to strengthen the reclassification petition.

In a PMA, it is difficult to pool data from various studies that use different protocols, because there may be differences in enrollment criteria, follow-up times, methodologies, and the outcome measures themselves. Such differences make it difficult to pool results and produce statistically meaningful analyses on specific performance characteristics of the particular device in question.

But RS Medical's petition is not about a specific device; it is about a generic type of device.

As such, positive outcomes from different test methodologies serve to strengthen the case for reclassification. Indeed, the fact that numerous studies conducted under disparate circumstances all yielded positive outcomes demonstrates that, as a general principle, the Non-Invasive Bone Growth Stimulator can be safe and effective.

The opposition is incorrect in its assertion that the studies cited in the reclassification petition do

¹² FDA has taken the position, upheld by the courts, that "sufficient information" for evaluating a petition "requires that valid scientific evidence in the record correlates the control of performance parameters to safe and effective use of the device. Thus, the question is whether the administrative record contains sufficient information for the agency to understand the device and sufficient evidence to demonstrate that factors determining the device's safety and effectiveness are controllable." *Ethicon*, 762 F. Supp. at 388.

not constitute valid scientific evidence. FDA defines "valid scientific evidence" as:

...evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. (21 C.F.R. §860.7(c)(2).)

RS Medical's original petition contains information on over 6,500 subjects¹³ that have been evaluated in 41 clinical studies with 28 (68.3%)¹⁴ of these studies being prospective in nature. This body of evidence clearly falls within FDA's definition of "valid scientific evidence." Moreover, the totality of data contained in the articles provided in the petition would convince any objective reviewer that the Non-Invasive Bone Growth Stimulator, as a type of device, can be safe and effective when regulated pursuant to Class II controls.

8. The comments state that RS Medical has not provided technical specifications for the devices that were the subject of the literature articles cited in the petition, thereby making it impossible for FDA to determine whether these devices can safely serve as predicates for new devices that would be subject to the 510(k) requirement.

The petition discusses the available literature from two perspectives. From one perspective, the data are reviewed in total to show that both the inductive coupling and capacitive coupling devices can be safe and effective, without specific regard as to which specific capacitive

¹³ This number is less than the originally reported 6,700 subjects (see page 0014 of the petition), as the findings from the study using the combined magnetic field device are not being included in this response.

¹⁴ The number of clinical studies (41) and prospective studies (28) reported in this response are less than the numbers originally reported (see page 0014 of the petition), as the findings from the study using the combined magnetic field device are not included.

coupling or inductive coupling device was being tested. But the petition also provides a separate analysis of data by the specific devices to be reclassified. The former set of data establish that the type of device can be safe and effective, and the latter show that the specific devices to be reclassified can serve as reasonable predicates.

9. The comments state that the petition does not include enough information about how a new device can be compared to a predicate device to ensure that it will perform in the same manner as its predicate.

The opposition's assertion is inaccurate. This information is provided on pages 20 through 24 of RS Medical's November 30, 2005 amendment. This discussion is lengthy and complex, and, therefore, will not be repeated here.

10. The comments insist that certain potential risks, e.g., interference from internal/external fixation devices, harm to electronic implants such as pacemakers, and potential biological effects at the cellular level, have not been adequately addressed in the petition.

The opposition's comment is without merit. RS Medical's November 30, 2006 amendment addresses all these risks.

The literature was reexamined to assess the risk of interference by internal/external fixation devices. RS Medical described the outcomes of studies cited in the petition when fixation devices were involved (pages 11 through 14). The data indicate that neither inductive coupling nor capacitive coupling devices are adversely affected by non-magnetic metallic fixation devices. The petition recommends that a warning be added to the labeling of Non-Invasive Bone Growth Stimulator to say that magnetic fixation devices may interfere with effective treatment by the device. The proposed 510(k) Guidance Document for the Non-Invasive BGS, which is one of the Class II special controls recommended in the RS Medical petition, describes this warning

(page 18 of the guidance). This issue would be addressed no differently were the device to remain in Class III.

RS Medical's November 30, 2006 amendment, states that RS Medical agrees that a Non-Invasive Bone Growth Stimulator could theoretically have an adverse effect on the performance of an electrical implant (page 11). Again, the petition recommends that a warning be added to the labeling of Non-Invasive Bone Growth Stimulator to say that the device may adversely affect the performance of electrical implants such as pacemakers. The proposed 510(k) Guidance Document for the Non-Invasive BGS describes this warning (page 18 of the guidance). Again, this issue would be addressed no differently were the device to remain in Class III.

In addition, the November 30, 2006 amendment discusses the literature applicable to biological risks. The petition notes that additional research may be appropriate to more fully explore certain limited questions, but the petition also notes that risks are obviously very low. The research being discussed is very academic and has not been, and will not be, required for PMA approval, even if the device were to remain in Class III.

11. The comments assert that the 510(k) review process is not designed to deal with new devices that may need to be identical to their predicates, and if a new device needs to be identical in order to be substantially equivalent, a 510(k) review is inappropriate.

Apparently, the opposition would like to disqualify new devices that are a virtual match to a predicate device from review through the 510(k) program. For years, the 510(k) program has been criticized in some quarters for allowing new devices with new technological features to be found substantially equivalent. Now, the opposition is presenting the notion that it is also inappropriate for a new device to be too much like its predicate. Congress, however, does not agree. The Report by the Committee on Interstate and Foreign Commerce on H.R. 11124 states:

The term “substantially equivalent” is not intended to be so narrow as to refer only to devices **that are identical** to marketed devices nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products. The committee believes that the term should be construed narrowly where necessary to assure the safety and effectiveness of a device but not so narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness. Thus, differences between “new” and marketed devices in materials, design, or energy source, for example, would have a bearing on the adequacy of information as to a new device’s safety and effectiveness, and such devices should be automatically classified into Class III. On the other hand, **copies of devices** marketed prior to enactment, or devices whose variations are immaterial to safety and effectiveness would not necessarily fall under the automatic classification scheme. (Page 36, emphasis added.)

This very well known quotation from the committee report establishes that identical devices are to be considered substantially equivalent.

12. The comments maintain that minor changes in this type of device can adversely affect safety or effectiveness, and this makes it unsuitable for 510(k) review and thus unsuitable for Class II.

The opposition states:

Numerous studies demonstrate that ostensible minor changes to BGS devices can adversely impact safety and effectiveness . . . These studies show that BGS devices are ill suited for a comparative determination of

“substantial equivalence” and that insufficient evidence exists to demonstrate that the proposed special controls are adequate.”¹⁵

Put in simpler terms, the argument amounts to an assertion that because one can make an unsafe or ineffective device as a result of a minor change, it is not possible to make an assessment of the substantial equivalence of any new device of this type. Although it is undisputed that changes to a device of this type can have adverse consequences, it is not clear why this fact should lead to the conclusion that the device is unsuitable for an evaluation of substantial equivalence. One can make an unsafe or ineffective device of any type. Thus, the logical extension of the opposition’s argument is that no device is suitable for marketing through 510(k) reviews.¹⁶ As a practical matter, seemingly minor changes can of course have significant safety or effectiveness consequences on many devices that are reviewed through the 510(k) process, but there is no serious argument that this fact makes the entire 510(k) process inappropriate. Rather, FDA routinely deals with the issue in a variety of ways, often by requiring a 510(k) to contain extensive testing information. In short, a submitter is required to establish that a difference in comparison to a predicate device has not adversely affected safety or effectiveness. Rather than advocating such an outlandish proposition, it may be that the opposition’s real argument is an unstated one, that seemingly minor changes may go unnoticed by the FDA during the course of a 510(k) review, and, as a result, an unsafe or ineffective device may reach the market. The comments, however, do not identify the flaws or omissions in the proposed 510(k) Guidance Document for Non-Invasive BGS -- which is one of the Class II special controls recommended in the RS Medical petition -- that would allow this to occur. RS Medical submits that there simply is no reason to believe that anything of importance will be overlooked in FDA’s review of a 510(k) that contains the information described in the proposed guidance document.

¹⁵ Comments of BGS Group, dated February 10, 2006, at 2.

<http://www.fda.gov/ohrms/dockets/dockets/05p0121/05p-0121-c000009-vol3.pdf>.

¹⁶ This is an absurd position that, we assume, is not taken when the opposition submits its own 510(k)s to FDA.

13. The comments state that these devices are unsuitable for 510(k) review because clinical data are necessary to provide a reasonable assurance of safety and effectiveness.

During the early implementation of the 1976 MDA, which introduced the 510(k) program, there was some controversy about whether clinical data should be required for 510(k)s, even though such data had sometimes been required during the 1970s and 1980s. Critics of this practice argued that authorizing FDA to require clinical data made a 510(k) too much like a PMA, even though the clinical data collected in 510(k)s tended to be more limited in scope than the data required in PMAs. In 1990, the SMDA resolved the question definitively by adding Section 513(i) to the Federal Food, Drug, and Cosmetic Act (FDCA), which provides:

(i)(1)(A) For purposes of determinations of substantial equivalence under subsection (f) and section 520(l), the term "substantially equivalent" or "substantial equivalence" means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device—

(i) has the same technological characteristics as the predicate device, or

(ii)(I) **has different technological characteristics** and the information submitted that the device is substantially equivalent to the predicate device contains information, **including appropriate clinical or scientific data if deemed necessary** by the Secretary or a person accredited under section 523, that demonstrates that the device is as safe and effective as a legally marketed device, and
(II) does not raise different questions of safety and effectiveness than the predicate device. (21 U.S.C. § 360c(i), emphasis added.)

The report by the Committee on Energy and Commerce on H.R. 3095, the House version of the adopted bill, explains the provision:

The Committee recognizes that the FDA does not always need clinical data to make a finding of substantial equivalence. It is the Committee's understanding that the FDA currently requests clinical data in less than 10% of the substantial equivalence determinations. The Committee believes that it is appropriate for the FDA to request such information when necessary. (Page 25)

It is not clear that clinical data will be needed for all 510(k)s for Non-Invasive Bone Growth Stimulators. In general, clinical data are required where differences between the new and predicate device merit the submission of testing data, and there are significant limitations associated with bench and animal testing. RS Medical's November 30, 2005 amendment to its petition establishes that the performance characteristics of existing approved Non-Invasive Bone Growth Stimulators can be duplicated in a testing laboratory. Bench testing should suffice if the signal is duplicated. Animal testing may be required in addition if there are minor deviations. In order to be prudent, the Agency may choose to require bench, animal and limited clinical data, or even extensive clinical data. None of these testing options falls outside the scope of the 510(k) review process, and such 510(k) review decisions are made by the Agency on a daily basis.

14. The comments state that these devices are unsuitable for 510(k) review because an FDA premarket inspection of manufacturing processes is necessary.

There are hundreds of Class II devices posing more risks than this device, and these devices are not subject to premarket manufacturing inspections. Moreover, an inspection program similar to the one used for PMA reviews can be directed at any device, regardless of whether the device is in Class I, II or III. For example, FDA can choose to inspect any specific device manufacturer at the same time it clears a 510(k).

15. The comments state that the devices proposed for reclassification differ significantly in mechanism of action, waveform, design, etc., and, therefore, require different special controls.

The petition submitted by RS Medical, as amended on November 30, 2005, identifies the special controls adequate to ensure the safety and effectiveness of both the capacitive coupling and inductive coupling devices included within the type of device defined within the petition. There are general controls and special controls. Given that both are needed, the device should be in Class II rather than Class I. The opposition has copies of the proposed controls, but aside from making their comment, to date they have not stated how the controls apply to one of the technologies and not to the other.

16. The comments state that RS Medical has not addressed the risk of thermal burns in a way that is appropriate and enforceable.

In response to an FDA inquiry about the possibility that thermal burns could occur if a user is sleeping while using the device and simultaneously charging the battery, RS Medical suggested a warning in the labeling. In addition, RS Medical stated that, as part of the special control guidance, the Agency could ask how each new manufacturer would address the issue in 510(k) submissions.

RS Medical also noted that the problem could be resolved with design changes that would prohibit simultaneous use and charging. RS Medical also suggested that multiple battery packs could enable the patient to have a charged battery pack continuously available, so the device could be used whenever the patient likes, even though use and charging could not occur simultaneously. RS Medical noted that the Agency could go so far as to require such a design as a special control.

In response, the opposition states:

RS Medical's proposed special control is inappropriate and unenforceable. Mandating design requirements is beyond the scope of FDA's regulation of device manufacturers in general and is certainly not within the scope of a device reclassification. Guidance documents issued by the Agency, such as the special control proposed by RS Medical, are not binding on FDA or the public. Thus, FDA could not require a BGS manufacturer to design its device with dual battery packs; and FDA could find a new BGS device to be substantially equivalent without these design features. Moreover, even the currently marketed BGS devices—the proposed predicate devices—do not meet these design criteria. Thus, RS Medical has failed to identify a special control that would adequately address the risk of thermal burns **and PMA review must be maintained.**¹⁷ (Emphasis added.)

The opposition is in error about a lack of FDA's authority. To illustrate the point, FDA has promulgated a regulation at 21 C.F.R. Part 898, entitled "Performance standard for electrode lead wires and patient cables," as a design standard for the identified devices. The regulation was promulgated under various cited authorities identified in the regulation and embedded in the FDCA. FDA has unquestionable authority to require such a battery pack design for the Non-Invasive Bone Growth Stimulator, just as it required certain design features for lead wires and patient cables. Moreover, because this reclassification process is being conducted under the rule-making provision of Section 513(e), any final rule could include certain design requirements, using the authorities in Section 514 of the FDCA. (21 U.S.C. § 360d.)

The opposition's comment states that not even the existing devices in Class III have solved this thermal burn problem, and they note that, as a result, new devices with the same flaw could be found substantially equivalent, and legally marketable, if the type of device is reclassified. Thus,

¹⁷ Comment of BGS Group, dated March 7, 2006, at 7.


the opposition is asserting, for some illogical reason, that classification in Class III has not addressed this issue. If indeed the designation as Class III cannot solve the thermal burn problem, then the proper conclusion is that the imposition of the standard making authority in Class II will be more effective in resolving this issue than the imposition of premarket approval in Class III.

17. The comments impugn the integrity of RS Medical's management team by asserting that RS Medical discussed with several PMA holders the possibility of withdrawing its petition if RS Medical could serve as a distributor of a PMA holder's approved device.

Business discussions routinely occur among competitors, or potential competitors, in the device industry. We will not further describe the nature of the conversations, but we must note that business-related discussions generally fall outside the purview of FDA oversight, and are entirely irrelevant to the issue at hand, i.e., whether Class II controls would provide a reasonable assurance of the safety and effectiveness of Non-Invasive Bone Growth Stimulators. The opposition's comments seem designed to impugn the integrity of the petitioner, and to perpetrate the erroneous notion that a request for reclassification is somehow an illegitimate ploy to avoid regulatory responsibilities.

We look forward to the Agency's review of this matter.

Sincerely,



Robert L. Sheridan

Attachment

The following comments do not represent the opinion of the FDA. FDA determines the questions for the panel.

The FDA questions for the panel are provided in Tab F of the previous mailing.

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May 12, 2006

BY MAIL

Mark Melkerson
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation (DGRND)
9200 Corporate Boulevard (HFZ-410)
Rockville, Maryland 20850

Re: Questions for the Orthopaedic and Rehabilitation Devices Panel Regarding the Proposed Reclassification of External Bone Growth Stimulator ("BGS") Devices

Dear Mr. Melkerson:

As you know, King & Spalding represents the BGS Reclassification Opposition Group ("BGS Group"), which was formed to address concerns that the proposed Class II regulatory requirements would be inadequate to assure the safety and effectiveness of new BGS devices. The BGS Group is comprised of the leading manufacturers in this device field—dj Orthopedics, Inc., EBI, L.P., and Orthofix Inc.

Through two meetings with members of CDRH and several written submissions, the BGS Group has urged FDA to refuse Panel review and deny the proposed down-classification of BGS devices from Class III to Class II because the reclassification petitioner has failed the following scientific and legal requirements: _____

- To define the technical specifications and tolerances for BGS devices;
- To define a "generic type" of BGS device for reclassification;
- To propose adequate special controls that would reasonably assure the safety and effectiveness of BGS devices; and
- To present sufficient "valid scientific evidence" demonstrating that the current Class III requirements are unnecessary and that the proposed special controls are adequate.

The Orthopaedic and Rehabilitation Devices Panel will consider the proposed reclassification of BGS devices at the June 2, 2006 meeting. It is critical that the Panel's deliberations and ultimate recommendation reflect the scientific and legal standards mandated

Mark Melkerson

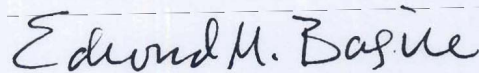
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for reclassification proceedings, as described above. To this end, the BGS Group submits the enclosed questions for the Panel's consideration. These questions cover the regulatory requirements for reclassification and the central characteristics of the BGS technologies. We believe that these questions are essential to ensure that the Panel bases its recommendations on the scientific and regulatory standards imposed by the Federal Food, Drug, and Cosmetic Act.

We look forward to the Panel meeting next month. Please do not hesitate to contact us with any questions.

Sincerely,

A handwritten signature in black ink that reads "Edward M. Basile". The signature is written in a cursive style with a horizontal line above it.

Edward M. Basile

Enclosure

cc: Dan Schultz
Donna Bea Tillman
Miriam Provost
Janet Scudiero

Proposed Reclassification of Bone Growth Stimulator Devices
Questions for the Orthopaedic and Rehabilitation Devices Panel

June 2, 2006

1. The petitioner defines the bone growth stimulators for reclassification as follows:

“A Non-invasive Bone Growth Stimulator provides stimulation through electrical and/or magnetic fields to promote osteogenesis to facilitate the healing of nonunion fractures and lumbar spinal fusions. The stimulation may be delivered through capacitive coupling (CC) with electrodes placed directly over the treatment site, or through pulsed electromagnetic fields (PEMF) with treatment coils placed into a brace or over a cast at the treatment site. The device is intended for use for 1) the treatment of established nonunion fractures acquired secondary to trauma (excluding vertebrae and flat bone), and 2) as an adjunct to the treatment of lumbar spinal fusion surgery for one or two levels. The device consists of an output waveform generator, either battery-powered or AC-powered, a user interface with visual and/or audible alarms, and electrodes or coils to deliver the stimulation. Accessories may include additional electrodes or coils, electrode accessories, electrode gel, positioning guides, connectors, batteries, battery chargers, belts and/or belt clips, carrying case, physician test meter, and others.”

The petitioner does not define the technical specifications for these devices because it believes that *“enough is known about the safety and effectiveness of these devices to make the setting of technical specifications unnecessary.”*

- **Please describe the**
 - **technical specifications, e.g., waveform frequency, amplitude, wavelength, etc.;**
 - **performance parameters, e.g., induced magnetic field, dynamic compensation, orientation, etc.; and**
 - **tolerances****defined by the petitioner for CC and PEMF devices intended to be used for non-unions and/or lumbar spinal fusions.**
- **Are these technical specifications, performance parameters, and tolerances adequate to assess whether a new BGS device is safe and consistently reproduces a clinically effective treatment signal for each of the proposed intended uses?**
 - **Please explain the basis for your conclusion.**

2. In order for a device to be reclassified, the petitioner must define a “generic type” of device for reclassification. FDA regulations define a “generic type” of device as “a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function,

or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.”

The petitioner proposes reclassification of external bone growth stimulators that work through capacitive coupling (“CC”) and pulsed electromagnetic field (“PEMF”) technology for the treatment of established non-union fractures acquired secondary to trauma (excluding vertebrae and flat bone) and as an adjunct to the treatment of lumbar spinal fusion surgery for one or two levels.

- **Describe how the petitioner has defined the following aspects of the CC bone growth stimulators proposed for reclassification:**
 - **purpose,**
 - **design,**
 - **materials,**
 - **energy source,**
 - **function, and**
 - **any other feature relating to safety and effectiveness.**
 - **Describe how the petitioner has defined the following aspects of the PEMF bone growth stimulators proposed for reclassification:**
 - **purpose,**
 - **design,**
 - **materials,**
 - **energy source,**
 - **function, and**
 - **any other feature relating to safety and effectiveness.**
 - **Do the descriptions above reflect a “generic type” containing devices that “do not differ significantly” in terms of their purpose, design, function, or other features?**
3. The petitioner may only rely on valid scientific evidence to support a proposed reclassification. Valid scientific evidence is defined as “evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.”

Valid scientific evidence does not include “isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions.”

- **Identify the studies provided by the petitioner that tested**
 - CC devices intended to be used for non-unions,
 - CC devices intended to be used for lumbar spinal fusions,
 - PEMF devices intended to be used for non-unions, and
 - PEMF devices intended to be used for lumbar spinal fusions.
- **For the studies identified above, please describe whether they were adequate in the following respects:**
 - waveform(s) of the device(s) tested,
 - sample size of the study,
 - inclusion/exclusion criteria,
 - treatment regimens,
 - durations of use,
 - definitions of clinical success,
 - definitions of radiological success, and
 - safety data.
- **Please state whether any of the studies cited by the petitioner are well-controlled clinical investigations. Specify the device and intended use that each investigation supports.**
- **Are the studies' treatment parameters similar or comparable so that the petitioner may draw conclusions based on a pooling of the studies' results?**
 - **Do the cited studies involving PEMF external bone growth stimulators support the down-classification of CC external bone growth stimulators?**
 - **Do the cited studies involving non-union uses support the down-classification of external bone growth stimulator devices intended to be used for spinal fusions?**
 - **For the petitioners purposes, is it appropriate to combine: a) sham-controlled, double-blinded, prospective studies (Level I), b) standard-of-care controlled (non-sham), prospective studies (Level II), c) historic-controlled, retrospective studies (Level III), and d) non-controlled, case series (Level IV) in order to draw safety and effectiveness conclusions?**

- In combining studies with various designs (i.e., Levels of evidence), how do confounding variables, differing definitions of success, different patient populations, and the different study designs affect the strength of the petitioner's conclusions?
 - Overall, has the petitioner presented sufficient valid scientific evidence to support the down-classification of
 - CC devices intended to be used for non-unions,
 - CC devices intended to be used for spinal fusions,
 - PEMF devices intended to be used for non-unions, and
 - PEMF devices intended to be used for spinal fusions?
4. The following table lists several risks to health FDA believes are associated with the use of external bone growth stimulators and the petitioner's proposed controls for addressing these risks.

Risk to Health	Proposed Special Control
Electrical Shock	<ul style="list-style-type: none"> • Preclinical Analysis and Testing • Electrical Equipment Safety • Software Life Cycle and Risk Management • Labeling
Burn	<ul style="list-style-type: none"> • Preclinical Analysis and Testing • Electrical Equipment Safety • Software Life Cycle and Risk Management • Labeling
Skin irritation and/or allergic reaction	<ul style="list-style-type: none"> • Biocompatibility analysis and testing • Labeling
Inconsistent or ineffective treatment	<ul style="list-style-type: none"> • Preclinical Analysis and Testing • Electrical Equipment Safety • Electromagnetic Compatibility • Software Life Cycle and Risk Management • Animal Studies • Clinical Studies • Labeling

Risk to Health	Proposed Special Control
Ineffective treatment due to magnetic fixation device	• Labeling
Damage to electrical implant	• Labeling
Biological effects of stimulation	• Labeling

- For the health risks identified in the table above, please state whether the special controls proposed by the petitioner would adequately address each risk.
 - For the proposed special controls that you conclude are adequate, please specify the valid scientific evidence that supports the adequacy of each special control.
- One of the proposed special controls to mitigate the risk of an ineffective or unsafe device is a clinical study. What types of differences among bone growth stimulator devices or changes to an existing device would necessitate a clinical study?

Please describe the elements and design of a clinical trial that would adequately evaluate the safety and effectiveness of external bone growth stimulator devices.
- Does this table identify all of the potential health risks associated with CC and PEMF external bone growth stimulators intended for the treatment of non-unions and/or lumbar fusion?
 - If not, what additional health risks should be considered?
 - What special controls would adequately address these additional health risks?
- Are the health risks associated with the treatment of established non-union fractures and the adjunctive treatment of lumbar spinal fusion “similar” enough that the petitioner’s proposed special controls for CC and PEMF devices constitute a “similar” set of regulatory controls that would assure the safety and effectiveness of new external bone growth stimulator devices? As discussed in question #2, the regulations require the petitioner to identify a “generic type” of bone growth stimulator device “for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.”

5. **Has the petitioner demonstrated that the current PMA review—requiring clinical studies demonstrating safety and effectiveness, and FDA’s premarketing assessment of manufacturing—are unnecessary to reasonably assure the safety and effectiveness of new CC and PEMF external bone growth stimulators?**
 - **Please specify the valid scientific evidence that supports your conclusion.**

COLUMBIA UNIVERSITY

IN THE CITY OF NEW YORK

DEPARTMENT OF BIOMEDICAL ENGINEERING

May 17,2006

Janet L. Scudiero
Center for Devices and Radiological Health (HFZ-410)
Food and Drug Administration
9200 Corporate Blvd.
Rockville,MD 20850

Subject: FDA Docket 2005P-O121/CCP 1
Comments in Support of the Reclassification of
Non-invasive Bone Growth Stimulators
Orthopaedic and Rehabilitation Devices Panel Mtg. June 2,2006

To whom it may concern:

I wish to convey my support for the reclassification of bone growth stimulators (BGS) from Class III to Class II. My reasons and my credentials follow.

I am Arthur Pilla, PhD, co-inventor of the first non-invasive BGS device to receive FDA approval for the treatment of non-union and delayed union bone fractures via the PMA process. I am also the co-founder of one of the current manufacturers of non-invasive BGS devices, with whom I severed all ties in the early 1980's. I have, however, actively continued my research on EMF effects of tissue growth and repair, which started in 1969, as a member of the faculty of the Departments of Biomedical Engineering at Columbia University, and Orthopaedics at Mount Sinai School of Medicine, both in New York, NY, as well as an industrial consultant.

In the early 1970's, we were, of course, overjoyed at the first clinical successes of non-invasive BGS treatments. However, there were many questions surrounding this success, particularly regarding the mechanism of action. Since that time the mechanism of action is much better understood, particularly for BGS devices which act via induced electric fields at the tissue target. In addition, hundreds of thousands of patients have been successfully treated with non-invasive BGS devices with no reported adverse effects over the past three decades.

I am attaching to this letter a final peer-reviewed preprint of my latest review article entitled "Mechanisms and Therapeutic Applications of Time-Varying and Static Magnetic Fields" (to appear in the Handbook of Biological Effects of Electromagnetic Fields, 3rd Edition. Barnes F, Greenebaum B, eds, CRC Press, 2006). Therein I report the latest clinical and basic research results on EMF tissue growth and repair. I have also attempted to provide enough evidence to

allow the reader to understand which characteristics of BGS waveforms are important for adequate dosimetry.

All clinical and basic biological effects obtained with the currently approved BGS devices are due either to the induced electric field, whether inductively or capacitively coupled, or to a combined static and low frequency magnetic field operating via the Lorentz force. The mechanism of action of the former is much better understood than that for the latter magnetic field devices. These mechanisms are sufficiently well understood that it is now clear the waveform characteristics of the FDA-approved BGS devices are not so unique that they preclude the possibility other waveforms could provide equal or even better physiological effects. For example, one such waveform is delivered by a BGS device produced in Italy. This device induces a signal with a peak electric field in the same range as the FDA-approved BGS devices, but, instead of a pulse burst repeating at 15/sec, it consists of a single asymmetrical bipolar pseudo rectangular pulse (0.3/7 msec) repeating at 75/sec. This BGS device has the necessary local regulatory approvals and has been extensively and successfully utilized for human fracture repair for at least 20 years in Europe. There are many double blind clinical studies showing efficacy with this device which are cited in my CRC review. There are also many failed clinical and basic studies using devices with waveform characteristics well outside those which are known, or could be predicted, to produce the desired biological and physiological effects. There are detailed analyses in my CRC review which can help explain why a given EMF waveform may or may not be effective, based, at least in part, on the degree to which the waveforms can modulate kinetics in the pertinent mechanistic pathways.

I have reviewed the draft of the Proposed FDA Guidance Document Entitled "Class II Special Controls Guidance Document: Contents of Premarket Notifications [510(k)s] for Non-invasive Bone Growth Stimulators" and am pleased to see it is already very comprehensive. I would like to offer the following suggestions to make it even more comprehensive. Documentation for all of the technical suggestions may be found in my CRC review.

- 1) **Section 4a Identification.** The definition of BGS could be modified to the following in light of the various PMA approvals over the years: **A Non-invasive Bone Growth Stimulator provides stimulation through electrical and/or magnetic fields to promote osteogenesis to facilitate the healing of nonunion fractures, failed fusions, congenital pseudoarthroses and lumbar and cervical spinal fusions. A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing. BGS is used as a spinal fusion adjunct to increase the probability of fusion success and as a nonoperative treatment for salvage of failed spinal fusions, where a minimum of nine months has elapsed since last surgery, and as an adjunct to cervical fusion surgery in patients at high risk for non-fusion.**
- 2) **Section 4b Classification.** Table 1 is incomplete and contains several errors. It could be changed using the following considerations (refer to my review for supporting references).
 - a) BGS devices which achieve their clinical results via induced electric fields do so whether the field is delivered via capacitive or inductive coupling.

- b) Coils for inductive coupling are typically placed over the treatment site. Electrodes for capacitive coupling are typically placed either flanking the treatment site, if accessible, or at some distance proximal and distal to provide for adequate depth of penetration.
- c) Peak induced current should not be used to define whether a signal is efficacious, only whether it is safe. This is because induced current/current density depends upon the electrical characteristics of the target which, in turn, depend upon individual anatomical factors, and which can change significantly during healing. The proposed Guidance Document does an excellent job to provide for the safety of BGS signals.
- d) The rectangular-type induced electric field waveforms already have approved ranges as follows: pulse widths of 10 - 300 usec; burst durations of 4 - 50 msec; and peak induced electric fields from 0.1-100 mV/cm.
- e) Effective peak induced electric fields for both capacitively and inductively coupled BGS waveforms range from 0.1-100 mV/cm provided this is achieved with waveforms having primary frequency components in the 0.01 - 100 kHz range.

In light of 2 above, Table 1 could then look like the following:

Signal type	Waveform	Tissue electric field
Sinusoidal	10-100 kHz Sine wave Continuous 5-50 % Duty cycle	0.1 -100 mV/cm
Pulse	Pulse duration: 1-300 fisec Burst duration: 0.1-50 msec Repetition rate: 1-20 Hz	0.1 -100 mV/cm
Combined Magnetic Fields	76.6 Hz sinusoidal 40 uT peak-to-peak AC magnetic field superimposed on 20 uT DC magnetic field	NA Magnetic field effect

I realize the ranges of proposed waveform values extend somewhat beyond those for currently approved BGS devices. However, they are given with the knowledge that the frequency and amplitude ranges are all within effective ranges, based on the current understanding of the mechanism of action. These parameter ranges may offer the FDA the capacity to provide manufacturers the opportunity to propose new, and perhaps improved, waveform characteristics for a particular BGS device. Of course, this may result in the requirement for supporting animal or clinical evidence to show the proposed signal is efficacious, but this is certainly manageable in the 510(k) context.

The remainder of the proposed Guidance Document is clear and to the point. It already goes a long way to provide manufacturers proper and reasonable guidance to submit a BGS device for 510(k) clearance. In spite of this, I am aware of the many objections to this reclassification

process orchestrated by, much to my chagrin, the major suppliers of BGS devices in the US. I am particularly distressed by the attempt to prove science, safety and efficacy of BGS devices by legal arguments. Many of these arguments either have no basis in the published literature or are simply wrong. The promulgation of arguments that mystify the now reasonably clear scientific and clinical evidence that has accrued on the use of BGS devices and raise vague and unfounded concerns about safety is a misguided legal tactic. Such arguments will impede the further adoption and innovation of BGS technology in clinical practice. More worrisome, and hopefully unintended, is the possibility that this same tactic will push BGS technology back into the dark ages of EMF therapy, an age many of us have toiled mightily to enlighten. It would be a travesty for the industry itself, even inadvertently, to blunt the innovative momentum that should accrue to a non-invasive, non-pharmacologic therapy that is clearly without adverse effects. There is more to be said, but this is not the place to provide further details of my many objections. I would be glad to provide these in an appendix if the Panel so desires.

I am certain the applications of EMF for tissue growth and repair would advance much more rapidly if BGS devices were reclassified into Class II. I remember how proud we all were 25 years ago that FDA approval for our BGS device immediately rendered the care of recalcitrant fractures significantly safer because they were non-surgical, non-invasive, non-pharmacologic and out-patient, and significantly reduced the cost of health care for this indication as well. The decades since have proven these devices to be safe and efficacious, but, as the understanding of the mechanisms of action has progressed, the design and approval of new and potentially more effective BGS devices, as well as new clinical applications, has simply not followed.

I applaud the FDA for their quest to reclassify BGS devices and stand ready to aid in this process in any manner.

Sincerely

A handwritten signature in black ink, appearing to read "Arthur A. Pilla". The signature is fluid and cursive, with the first name "Arthur" being more prominent.

Arthur A Pilla, PhD

May 18, 2006

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: FDA Docket 2005P-0121/CCP; Two Additional Literature Articles

Dear Sir or Madam:

Please file the enclosed two journal articles with the docket cited above. One article is a follow-up to an article already submitted. The other is a new finding regarding the mechanism of action for the capacitive coupled signal.

Sincerely,

Natalia Owen, M.S., CCRA
Clinical Research Manager
(800) 929-6581
nowen@rsmedical.com